

4-AMINOQUINOLINE-3-CARBOXAMIDE DERIVATIVES AS PDE4 INHIBITORS

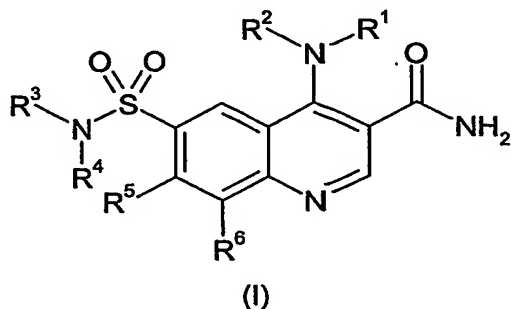
The present invention relates to quinoline compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the quinoline compounds in therapy, for example as inhibitors of phosphodiesterases and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

WO 02/20489 A2 (Bristol-Myers-Squibb Company) discloses 4-aminoquinoline derivatives wherein the 4-amino group NR^4R^5 may represent an acyclic amino group wherein R^4 and R^5 may each independently represent hydrogen, alkyl, cycloalkyl, aryl, heteroaryl etc.; NR^4R^5 may alternatively represent an aliphatic heterocyclic group. The compounds are disclosed as inhibitors of cGMP phosphodiesterase, especially type 5 (PDE5).

EP 0 480 052 (Otsuka Pharmaceutical Co. Ltd.) discloses 4-aminoquinoline-3-carboxamides wherein the 4-amino group NHR^4 may represent an amino group wherein R^4 represents phenyl, tetrahydronaphthyl or naphthyl, optionally substituted with alkyl, halogen, alkoxy etc.; and the 3-carboxamide group CONR^2R^3 represents a primary, secondary or tertiary carboxamide group. The compounds are disclosed as inhibitors of gastric acid secretion, and as cytoprotective agents; inhibition of the ATPase activated by H^+ and K^+ at the gastric wall cells is also disclosed.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

According to the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

R¹ is

Aryl optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halogen, C₁₋₆alkylCO-, -(CH₂)_mOH, -CN, R⁷R⁸N-;

5 Aryl fused to a C₄₋₇cycloalkyl ring;

Aryl fused to a heterocyclyl ring;

10 Heteroaryl wherein the heteroaryl is optionally substituted by one or more substituents selected from: C₁₋₆alkyl, N-oxide, C₁₋₆alkoxy;

Heterocyclyl.

R² is hydrogen or C₁₋₆alkyl;

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R³ is

Hydrogen;

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C₁₋₆alkyl optionally substituted by one or more substituents selected from: heterocyclyl (itself optionally substituted by C₁₋₆alkyl), R⁹R¹⁰NCO-, R¹¹CONR¹²-, C₁₋₆alkylSO₂NR¹³-, C₁₋₆alkoxy, R¹⁴R¹⁵N-;

C₃₋₇cycloalkyl;

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Aryl or aryl(C₁₋₆alkyl) wherein the aryl is optionally substituted by one or more substituents selected from: C₁₋₆alkyl, C₁₋₆alkoxy, halogen, R¹⁶R¹⁷NCO-;

Aryl fused to C₄₋₇cycloalkyl, wherein the cycloalkyl is optionally substituted by =O;

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Heteroaryl or heteroaryl(C₁₋₆alkyl), wherein the heteroaryl is optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halogen;

Heterocyclyl optionally substituted by one or more C₁₋₆alkyl, C₁₋₆alkylCO-, C₁₋₆alkylSO₂-, R¹⁸R¹⁹NCO-, C₁₋₆alkoxyCO-;

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R⁴ is hydrogen or C₁₋₆alkyl;

R³ and R⁴ together with the nitrogen atom to which they are attached may form a heterocyclyl ring, which is optionally substituted by one or more substituents selected from C₁₋₆alkyl (optionally substituted by one or more OH or C₁₋₆alkoxy groups), C₁₋₆alkoxy, C₁₋

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alkoxyCO-, C₃₋₇cycloalkyl (optionally substituted by OH), C₁₋₆alkylCO-, C₁₋₆alkylSO₂-, OH, -(CH₂)_mNR²⁰R²¹, -(CH₂)_mCONR²²R²³, -(CH₂)_mNR²⁴COR²⁵, C₁₋₆alkoxyC₁₋₄alkyl, arylCO-heteroaryl, heteroarylC₁₋₄alkyl, heteroarylCO.

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R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, fluorine, chlorine, or bromine;

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R⁷⁻²⁵ all independently represent hydrogen, C₁₋₆ alkyl;

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

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R¹⁶ and R¹⁷ together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

R¹⁸ and R¹⁹ together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

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R²⁰ and R²¹ together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

R²² and R²³ together with the nitrogen atom to which they are attached may form a heterocyclyl ring;

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As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl chain containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl. A C₁₋₄alkyl group is preferred, for example methyl, ethyl or isopropyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms, for example, trifluoromethyl.

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As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, prop-1-oxy, prop-2-oxy, but-1-oxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy. A C₁₋₄alkoxy group is preferred, for example methoxy or ethoxy. The said alkoxy groups may be optionally substituted with one or more fluorine atoms, for example, trifluoromethoxy.

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As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C₃₋₇cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C₃₋₆cycloalkyl group is preferred, for example cyclopentyl.

When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic carbocyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl, optionally fused to a C₄₋₇cycloalkyl or heterocyclyl ring.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic five- to seven- membered heterocyclic aromatic ring containing one or more heteroatoms selected from oxygen, nitrogen and sulfur. In a particular aspect such a ring contains 1-3 heteroatoms. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. The terms "heteroaryl ring" and "heteroaryl" also refer to fused bicyclic heterocyclic aromatic ring systems containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the fused rings each have five or six ring atoms. Examples of fused heterocyclic aromatic rings include, but are not limited to, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothieryl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl and benzothiadiazolyl. The heteroaryl may attach to the rest of the molecule through any atom with a free valence.

As used herein, the term "heterocyclyl" refers to a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. In a particular aspect such a ring contains 1 or 2 heteroatoms. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazepinyl, azepinyl, tetrahydrofuranyl, tetrahydropyranyl, and 1,4-dioxanyl.

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. Particularly preferred halogens are fluorine and chlorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

In a preferred embodiment, R¹ is selected from

Aryl optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy-, halogen, -CN;

Aryl fused to a heterocyclyl ring;

Heteroaryl optionally substituted by one or more substituents selected from: C₁₋₆alkyl.

In a preferred embodiment R¹ is selected from

Phenyl optionally substituted by one or more substituents selected from methyl, methoxy, fluoro, chloro, cyano;

Dihydrobenzofuranyl;

Indazolyl or benzimidazolyl optionally substituted by methyl.

Representative examples of R¹ include 3-(methoxy)phenyl, 3-chlorophenyl, 3-fluorophenyl, 3-cyanophenyl, 3-methylphenyl, 4-fluoro-3-(methoxy)phenyl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-indazol-6-yl and 2,3-dihydro-1-benzofuran-4-yl.

In a preferred embodiment, R² is hydrogen.

Representative examples of R² include hydrogen.

In a preferred embodiment R³ is selected from

C₁₋₆alkyl optionally substituted by one or more C₁₋₆alkoxy groups;

C₃₋₇cycloalkyl;

Heterocyclyl.

In a preferred embodiment R^3 is selected from

C_{1-6} alkyl optionally substituted by one or more substituents selected from heterocyclyl, C_{1-6} alkoxy;

C_{3-7} cycloalkyl;

Heterocyclyl.

In a preferred embodiment R^3 is selected from

C_{1-3} alkyl optionally substituted by one C_{1-2} alkoxy group or a 5 to 7 membered saturated ring containing one or two heteratoms selected from nitrogen or oxygen;

C_{3-5} cycloalkyl;

5 to 7 membered saturated ring containing one heteroatom which is oxygen.

Representative examples of R^3 include methyl, 2-(methyloxy)ethyl, tetrahydro-2H-pyran-4-yl, cyclopropyl, N-pyrrolidinethyl and N-morpholinethyl.

In a preferred embodiment R^4 is hydrogen or C_{1-6} alkyl;

Representative examples of R^4 include hydrogen and methyl.

In a particularly preferred embodiment, R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring, optionally substituted by C_{1-6} alkyl (optionally substituted by one or more C_{1-6} alkoxy groups), C_{1-6} alkylCO, C_{1-6} alkylSO₂; - (CH₂)_mCONR²²R²³, heteroaryl.

In a particularly preferred embodiment, R^3 and R^4 together with the nitrogen atom to which they are attached may form a heterocyclyl ring, optionally substituted by one or more substituents selected from C_{1-6} alkyl (optionally substituted by one or more C_{1-6} alkoxy groups), C_{1-6} alkylCO, C_{1-6} alkylSO₂; -(CH₂)_mCONR²²R²³, -(CH₂)_mNR²⁰R²¹, heteroaryl.

In a particularly preferred embodiment, R^3 and R^4 together with the nitrogen atom to which they are attached may form a 5 or 6 membered heterocyclyl ring, optionally substituted by one or more substituents selected from C_{1-3} alkyl (optionally substituted by

one or more C₁₋₂alkoxy groups), C₁₋₃alkylCO, C₁₋₃alkylSO₂; -CON(CH₃)₂, -N(CH₃)₂, pyrazinyl, pyridinyl.

Representative examples wherein R³ and R⁴ together with the nitrogen atom to which they are attached may form a heterocyclyl ring include 1-piperidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, 4-acetyl-1-piperazinyl, 4-(methylsulfonyl)-1-piperazinyl, 4-(2-pyrazinyl)-1-piperazinyl, 4-[2-(methyloxy)ethyl]-1-piperazinyl, 4-[(dimethylamino)carbonyl]-1-piperazinyl, 1-pyrrolidinyl and 4-(dimethylamino)-1-piperidinyl.

10 In a preferred embodiment R⁵ represents hydrogen.

Representative examples of R⁵ include hydrogen.

In a preferred embodiment R⁶ represents hydrogen or C₁₋₆alkyl.

15 Representative examples of R⁶ include hydrogen and methyl.

In a preferred embodiment there exists a subgroup of formula (IA) wherein

- 20 R¹ is selected from
phenyl optionally substituted by one or more substituents selected from methyl, methoxy, fluoro, chloro, cyano;
dihydrobenzofuranyl;
indazolyl or benzimidazolyl optionally substituted by methyl;
- 25 R² is hydrogen;
- R³ is selected from
C₁₋₃alkyl optionally substituted by one C₁₋₂alkoxy group or a 5 to 7 membered saturated ring containing one or two heteratoms selected from nitrogen or oxygen;
30 C₃₋₅cycloalkyl;
5 to 7 membered saturated ring containing one heteroatom which is oxygen;
- R⁴ is hydrogen or C₁₋₆alkyl;
- R⁵ is hydrogen;
- 35 R⁶ is hydrogen or C₁₋₆alkyl.

In a preferred embodiment there exists a subgroup of formula (IB) wherein

R¹ is selected from
 phenyl optionally substituted by one or more substituents selected from methyl,
 methoxy, fluoro, chloro, cyano;
 dihydrobenzofuranyl;
 5 indazolyl or benzimidazolyl optionally substituted by methyl;

R² is hydrogen;

R³ and R⁴ together with the nitrogen atom to which they are attached may form a
 10 5 or 6 membered heterocyclyl ring, optionally substituted by one or more
 substituents selected from C₁₋₃alkyl (optionally substituted by one or more C₁₋₂
 alkoxy groups), C₁₋₃alkylCO, C₁₋₃alkylSO₂, -CON(CH₃)₂, -N(CH₃)₂, pyrazinyl,
 pyridinyl;

R⁵ is hydrogen;

R⁶ is hydrogen or C₁₋₆alkyl.

It is to be understood that the present invention covers all combinations of substituent
 20 groups referred to hereinabove.

It is to be understood that the present invention covers all combinations of particular and
 preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the examples
 and their pharmaceutically acceptable salts. Specific examples which may be mentioned
 include:

Example 2: 6-[(dimethylamino)sulfonyl]-4-[[3-(methyloxy)phenyl]amino]-3-
 quinolinecarboxamide

Example 5: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-(4-morpholinylsulfonyl)-3-
 quinolinecarboxamide

Example 11: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-[[4-fluoro-3-(methyloxy)phenyl]amino]-
 3-quinolinecarboxamide

Example 12: 4-[[4-fluoro-3-(methyloxy)phenyl]amino]-6-[[4-(methylsulfonyl)-1-
 35 piperazinyl]sulfonyl]-3-quinolinecarboxamide

Example 13: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-(2,3-dihydro-1-benzofuran-4-ylamino)-3-
 quinolinecarboxamide

Example 14: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[[4-(methylsulfonyl)-1-
 piperazinyl]sulfonyl]-3-quinolinecarboxamide

Example 17: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[(dimethylamino)sulfonyl]-3-quinolinecarboxamide

Example 21: 6-[(4-[(dimethylamino)carbonyl]-1-piperazinyl)sulfonyl]-4-[[4-fluoro-3-(methoxy)phenyl]amino]-3-quinolinecarboxamide

5 Example 22: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[[4-(2-pyrazinyl)-1-piperazinyl)sulfonyl]-3-quinolinecarboxamide

Example 23: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[(4-[(dimethylamino)carbonyl]-1-piperazinyl)sulfonyl]-3-quinolinecarboxamide

10 Example 29: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[(tetrahydro-2H-pyran-4-ylamino)sulfonyl]-3-quinolinecarboxamide
and pharmaceutically acceptable salts thereof.

Further specific examples which may be mentioned include:

15 Example 42: 4-[[4-fluoro-3-(methoxy)phenyl]amino]-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

Example 43: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

20 Example 44: 8-methyl-4-[(3-methylphenyl)amino]-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

Example 45: 4-[(3-fluorophenyl)amino]-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

Example 46: 4-[(3-cyanophenyl)amino]-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

25 Example 48: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-[[4-(dimethylamino)-1-piperidinyl)sulfonyl]-3-quinolinecarboxamide

Example 50: 4-[(3-chlorophenyl)amino]-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

30 Example 51: 8-methyl-4-[(1-methyl-1H-indazol-6-yl)amino]-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

Example 52: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-8-methyl-4-[(3-methylphenyl)amino]-3-quinolinecarboxamide

Example 53: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-[[4-fluoro-3-(methoxy)phenyl]amino]-8-methyl-3-quinolinecarboxamide

35 Example 54: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-3-quinolinecarboxamide
and pharmaceutically acceptable salts thereof.

Preferred specific examples which may be mentioned include:

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Example 23: 4-(2,3-dihydro-1-benzofuran-4-ylamino)-6-({4-[(dimethylamino)carbonyl]-1-piperazinyl)sulfonyl)-3-quinolinecarboxamide

Example 51: 8-methyl-4-[(1-methyl-1H-indazol-6-yl)amino]-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

- 5 Example 54: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-(2,3-dihydro-1-benzofuran-4-ylamino)-8-methyl-3-quinolinecarboxamide
and pharmaceutically acceptable salts thereof.

Further preferred specific examples which may be mentioned include:

- 10 Example 11: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-[[4-fluoro-3-(methyloxy)phenyl]amino]-3-quinolinecarboxamide

Example 13: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-(2,3-dihydro-1-benzofuran-4-ylamino)-3-quinolinecarboxamide

- 15 Example 50: 4-[(3-chlorophenyl)amino]-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

Example 52: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-8-methyl-4-[(3-methylphenyl)amino]-3-quinolinecarboxamide

- 20 Example 53: 6-[(4-acetyl-1-piperazinyl)sulfonyl]-4-[[4-fluoro-3-(methyloxy)phenyl]amino]-8-methyl-3-quinolinecarboxamide
and pharmaceutically acceptable salts thereof.

- Salts of the compounds of the present invention are also encompassed within the scope of the invention. Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, *p*-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, acetate, fumarate, citrate, tartrate, benzoate, *p*-toluenesulfonate, methanesulfonate or naphthalenesulfonate salt. A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base, optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration. Other non-pharmaceutically acceptable salts, eg. oxalates or trifluoroacetates, may be used, for example in the isolation of compounds of the invention, and are included

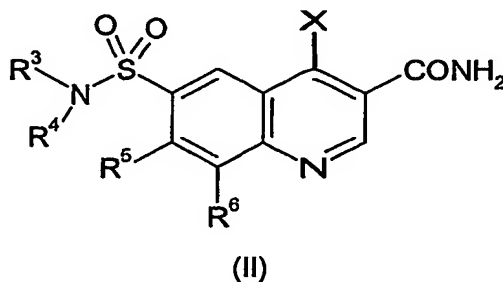
within the scope of this invention. The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I). Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

Process a

Compounds of formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined above may be prepared from compounds of formula (II);

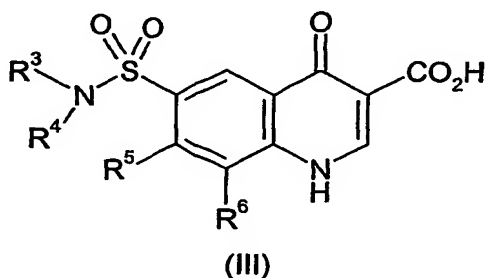


wherein R^3 , R^4 , R^5 and R^6 are as defined above, and X represents a halogen atom, by treatment with an amine of formula R^1R^2NH , wherein R^1 and R^2 are as defined above.

Suitable conditions for process a) include stirring in a suitable solvent such as acetonitrile or a mixture of acetonitrile and *N,N*-dimethylformamide, at a suitable temperature, such as between room temperature and the reflux temperature of the solvent, for example at 80°C, optionally in the presence of a suitable base such as *N,N*-diisopropylethylamine.

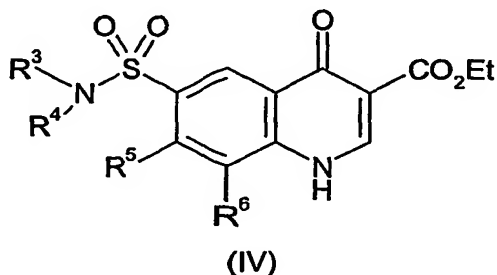
Alternatively, process a) may be carried out under microwave irradiation, at a suitable power such as 150W, in a suitable solvent such as *N*-methyl-2-pyrrolidinone, at a suitable temperature such as 60-200°C, for example at 150°C. Process a) may alternatively be carried out in the presence of an acid catalyst, such as pyridine hydrochloride or concentrated hydrochloric acid, in a suitable solvent such as ethanol, at a suitable temperature such as the reflux temperature of the solvent.

Compounds of formula (II), wherein R³, R⁴, R⁵, R⁶, and X are as defined above, may be prepared from compounds of formula (III);



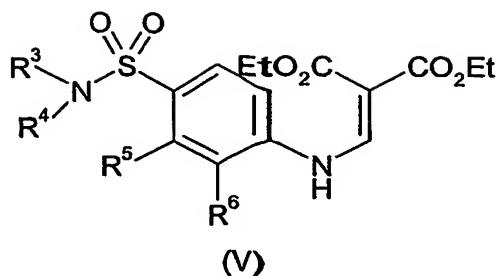
wherein R³, R⁴, R⁵ and R⁶ are as defined above, by treatment with a suitable halogenating agent, such as a chlorinating agent, for example thionyl chloride, in the presence of a suitable catalyst such as *N,N*-dimethylformamide, followed by treatment with ammonia under suitable conditions, such as 880 ammonia at room temperature.

Compounds of formula (III), wherein R³, R⁴, R⁵ and R⁶ are as defined above, may be prepared from compounds of formula (IV);



wherein R³, R⁴, R⁵ and R⁶ are as defined above, by hydrolysis with a suitable base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at a suitable temperature such as room temperature.

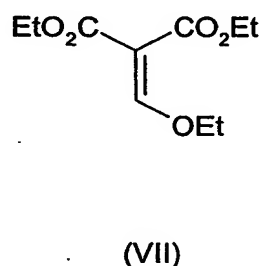
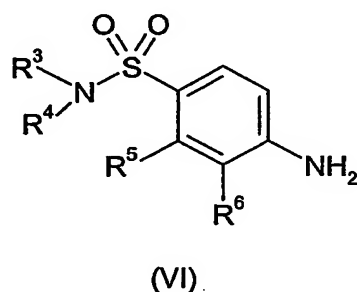
Compounds of formula (IV), wherein R³, R⁴, R⁵ and R⁶ are as defined above, may be prepared from compounds of formula (V);



- 5 wherein R^3 , R^4 , R^5 and R^6 are as defined above, by heating in a suitable solvent, such as diphenyl ether, at a suitable temperature such as 200-300°C, for example at 250°C.

Compounds of formula (V), wherein R^3 , R^4 , R^5 and R^6 are as defined above, may be prepared from compounds of formula (VI), wherein R^3 , R^4 , R^5 and R^6 are as defined above, and the compound of formula (VII);

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- 15 Suitable conditions include heating together compounds of formulae (VI) and (VII) in the absence of solvent, at a suitable temperature, such as 60-150°C, for example at 100°C. Alternative conditions include heating together compounds of formulae (VI) and (VII) under microwave irradiation, for example at 150W power, at a suitable temperature such as 100-200°C, for example at 150°C, for a suitable time such as 15 minutes.

20 Preparation of compounds of formula (III), (IV) and (V) wherein R^3R^4N represents dimethylamino, diethylamino, or di(*n*-propylamino), $R^5 = H$ and $R^6 = H$; or wherein R^3 and R^4 together with the nitrogen to which they are attached represent 1-piperidiny, 4-morpholinyl and 4-methyl-1-piperazinyl, $R^5 = H$ and $R^6 = H$ have been previously described in patent ZA 6706075 (1968).

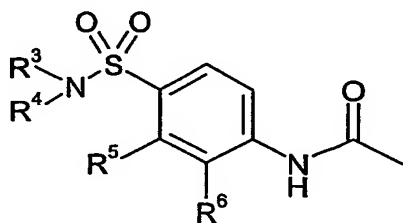
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The compounds of formula (VI) wherein R^5 and R^6 both represent hydrogen and R^3 and R^4 both represent methyl (SALOR); or wherein R^5 and R^6 both represent hydrogen and R^3

and R⁴ together with the nitrogen to which they are attached represent morpholine (Maybridge Int) or piperidine (Maybridge Int) are commercially available.

The compound of formula (VII) is commercially available (Aldrich).

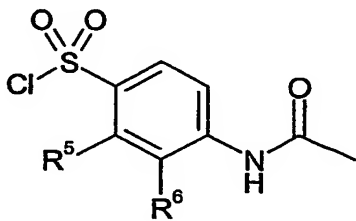
Compounds of formula (VI), wherein R³, R⁴, R⁵ and R⁶ are as defined above, may be prepared from compounds of formula (VIII);



(VIII)

wherein R³, R⁴, R⁵ and R⁶ are as defined above, by hydrolysis with a suitable base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at a suitable temperature such as 80°C.

Compounds of formula (VIII), wherein R³, R⁴, R⁵ and R⁶ are as defined above, may be prepared from compounds of formula (IX);



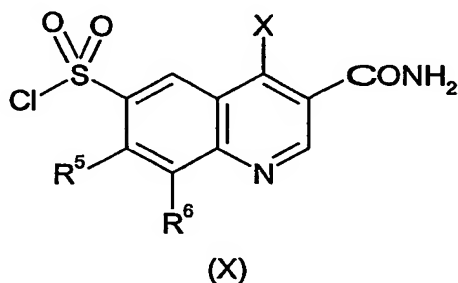
(IX)

wherein R⁵ and R⁶ are defined above, by treatment with an amine of formula R³R⁴NH, wherein R³ and R⁴ are as defined above, and a suitable base such as sodium acetate, in a suitable solvent such as ethanol, with a suitable amine, at a suitable temperature such as 0°C.

Compounds of formula (IX), wherein R⁵ and R⁶ are as defined above, are either known compounds (for example available from commercial suppliers such as Aldrich) or may be

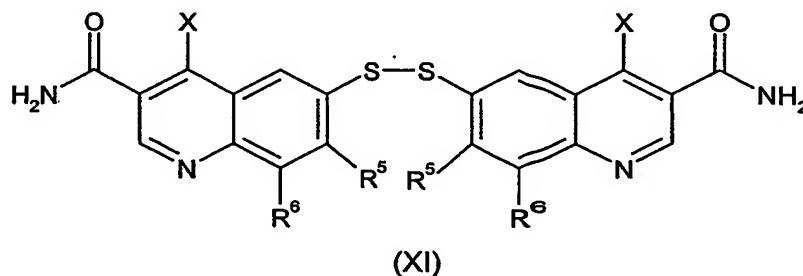
prepared by conventional means. The compound of formula (IX) wherein R^5 and R^6 are hydrogen is commercially available (Fluka).

- 5 Compounds of formula (II), wherein R^3 , R^4 , R^5 , R^6 and X are as defined above may alternatively be prepared from compounds of formula (X);



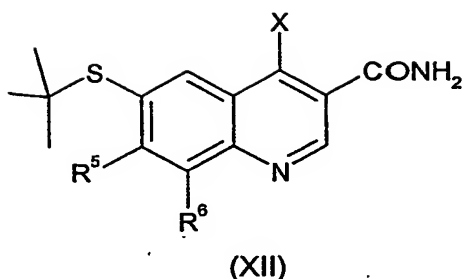
- 10 wherein R^5 , R^6 and X are as defined above, by treatment with an amine of formula R^3R^4NH wherein R^3 and R^4 are as defined above. Suitable conditions include stirring in a suitable solvent such as dichloromethane, or a mixture of dichloromethane and *N,N*-dimethylformamide, at a suitable temperature such as between 0°C and 20°C in the presence of a suitable base such as *N,N*-diisopropylethylamine.

- 15 Compounds of formula (X), wherein R^5 , R^6 and X are as defined above, may be prepared from compounds of formula (XI);



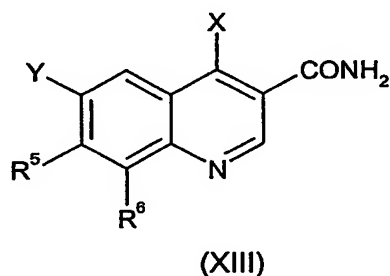
- 20 wherein R^5 , R^6 and X are defined above, by treatment with chlorine. Suitable conditions include stirring in a suitable solvent such as aqueous acetic acid, at a suitable temperature, such as 20°C .

- 25 Compounds of formula (XI) wherein R^5 , R^6 and X are as defined above, may be prepared from compounds of formula (XII);



5 wherein R⁵, R⁶ and X are defined above, by treatment with a suitable acid, such as trifluoroacetic acid, in the presence of a suitable oxidising agent, such as phenyl sulphoxide and a suitable silane, such as methyltrichlorosilane, at a suitable temperature such as 0°C.

10 Compounds of formula (XII) wherein R⁵, R⁶ and X are as defined above, may be prepared from compounds of formula (XIII):

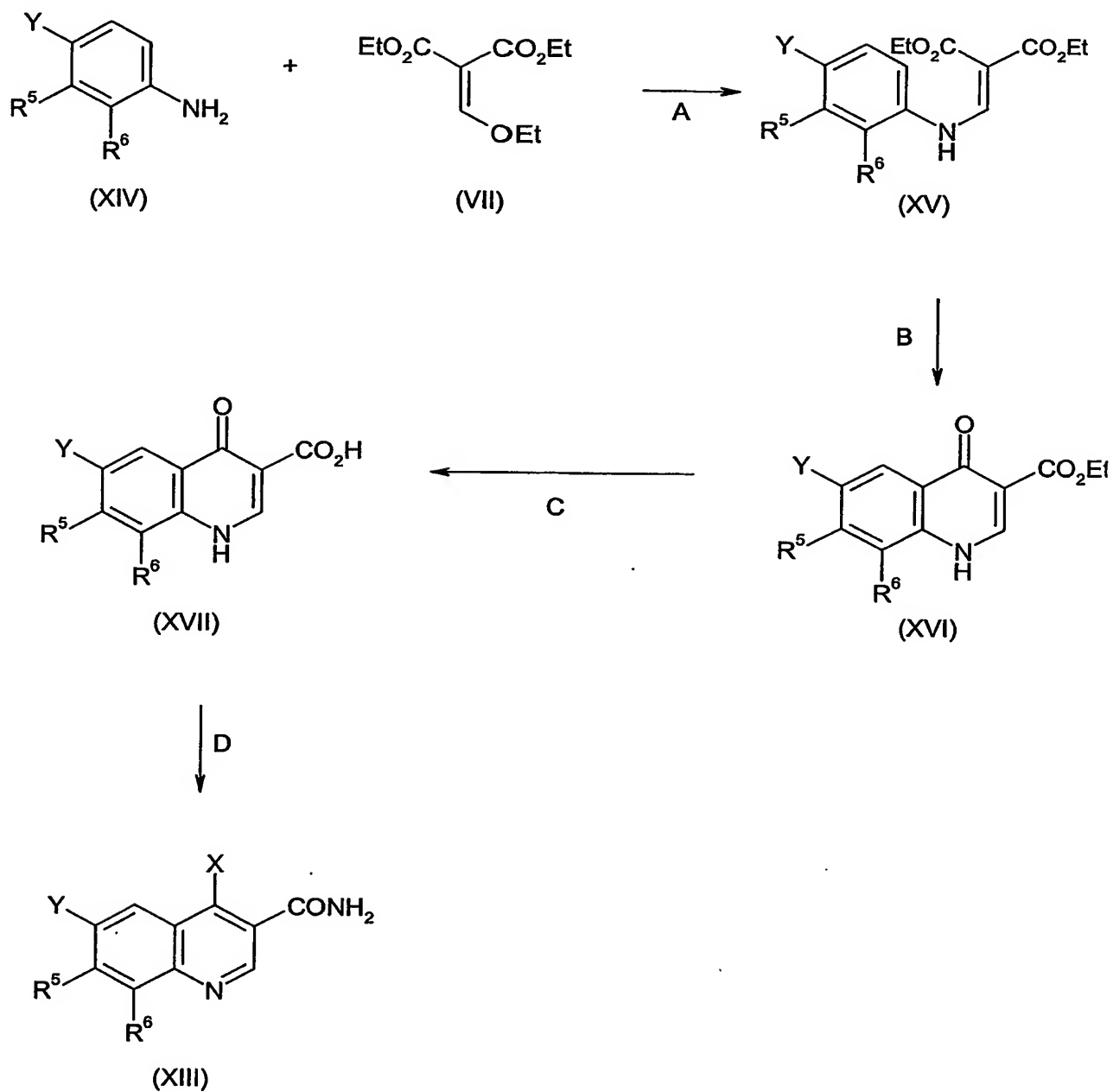


15 wherein R⁵, R⁶, and X are as defined above and Y is iodine or bromine, by treatment with a suitable tin compound such as (*tert*-butylsulphonyl)tributyltin in a suitable solvent such as toluene, at a suitable temperature, such as 60-120°C, for example 110°C, in the presence of a suitable catalyst such as a palladium catalyst, for example tetrakis(triphenylphosphine) palladium (0).

20 The compounds of formula (XIII) may be prepared according to the following synthetic scheme, wherein R⁵, R⁶, X and Y are as defined above:

25

SCHEME 1



Suitable conditions for the reactions of Scheme 1 are: (A) heating together compounds of formulae (XIV) and (VII) in the absence of solvent, at a suitable temperature, such as 60-100°C, for example at 80°C; (B) heating compounds of formula (XV) in a suitable solvent,

such as diphenyl ether, at a suitable temperature such as 200-300°C, for example at 250°C; (C) hydrolysis of compounds of formula (XVI) with a suitable base, such as aqueous sodium hydroxide, in a suitable solvent, such as ethanol, at a suitable temperature such as room temperature; (D) treatment of compounds of formula (XVII) with a suitable halogenating agent, such as a chlorinating agent, for example thionyl chloride, in the presence of a suitable catalyst such as *N,N*-dimethylformamide, followed by treatment with ammonia under suitable conditions, such as 880 ammonia at room temperature.

- 10 Preparation of the compounds of formulae (XV) and (XVI) wherein Y represents iodine and R⁵ and R⁶ both represent hydrogen have been previously described in: Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (2002), 41B(3), 650-652. Preparation of the compound of formula (XVII) wherein Y represents iodine and R⁵ and R⁶ both represent hydrogen has been previously described in: PCT Int. Appl. (1999), WO 9932450 A1.

Compounds of formulae (XIV), R¹R²NH and R³R⁴NH, wherein R¹, R², R³, R⁴, R⁵, R⁶ and Y are as defined above, are either known compounds (for example available from commercial suppliers such as Aldrich) or may be prepared by conventional means.

- 20 Compounds of formulae R¹R²NH and R³R⁴NH may contain amine or acid groups which are suitably protected. Examples of suitable protecting groups and the means for their removal can be found in T. W. Greene and P. G. M. Wuts 'Protective Groups in Organic Synthesis' (3rd Ed., J. Wiley and Sons, 1999). Addition or removal of such protecting groups may be accomplished at any suitable stage in the synthesis of compounds of formula (I).

Process b

- 30 Compounds of formula (I) may also be prepared by a process of interconversion between compounds of formula (I). Processes of interconversion between compounds of formula (I) may include, for example oxidation, reduction, alkylation, dealkylation, acylation, sulfonylation or substitution.

Process c

- 35 Compounds of formula (I) may also be prepared by a process of deprotection of protected derivatives of compounds of formula (I). Examples of suitable protecting groups and the means for their removal can be found in T. W. Greene and P. G. M. Wuts 'Protective Groups in Organic Synthesis' (3rd Ed., J. Wiley and Sons, 1999).

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the conditions described herein and/or for use as a phosphodiesterase inhibitor, e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are believed to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis (seasonal or perennial), vasomotor rhinitis, nasal polyps, allergic conjunctivitis, vernal conjunctivitis, occupational conjunctivitis, infective conjunctivitis, eosinophilic syndromes, eosinophilic granuloma, psoriasis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, multiple sclerosis, memory impairment (including Alzheimer's disease) pain or depression.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, asthma, rheumatoid arthritis, allergic rhinitis, atopic dermatitis or psoriasis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD including chronic bronchitis and emphysema, asthma or allergic rhinitis in a mammal (e.g. human). PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, **59**(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, **5**, 432-438; and refs cited therein) and COPD (e.g. see S.L. Wolda, *Emerging Drugs*, 2000, **5**(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, **5**, 432-438; and refs cited therein). COPD is often characterised

by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319).

5 PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

10 PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and refs cited therein). See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and refs cited therein for atopic dermatitis use.

15 PDE4 inhibitors have been suggested as having analgesic properties and thus being effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

20 In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

25 PDE4 inhibitors such as rolipram have been suggested as having antidepressant properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; and H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595).

30 For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

35 The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

40 The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or

intramuscular), inhaled, nasal, transdermal or rectal administration, or as topical treatments (e.g. lotions, solutions, creams, ointments or gels). Accordingly, the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous or intramuscular), topical, inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for topical, inhaled or oral administration, e.g. to a mammal such as a human. Inhaled administration involves topical administration to the lung, e.g. by aerosol or dry powder composition.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a solution, a syrup, a suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, aqueous ethanol or aqueous glycerine, or an oil, or a non-aqueous solvent, such as a surfactant, such as polyethylene glycol. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion, suspension or solution can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous solution, aqueous gum or an oil and the dispersion, suspension or solution then filled into a soft or hard gelatin capsule.

The compounds of formula (I) and/or the pharmaceutical composition may be administered by a controlled or sustained release formulation as described in WO 00/50011.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil.

Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

5 Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size
10 of the size-reduced (e.g. micronised) compound or salt is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-
15 aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of
20 the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include
25 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may
30 also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is
35 preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) or salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, cellobiose octaacetate and/or metals salts of stearic acid
40 such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or

salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of e.g. the dry powder composition can be administered by inhalation via the device such as the DISKUSTM device, marketed by GlaxoSmithKline. The DISKUSTM inhalation device is for example described in GB 2242134 A, and in such a device at least one container for the pharmaceutical composition in powder form (the container or containers preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: a means of defining an opening station for the said container or containers; a means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

For application topically to the skin, the compound of formula (I) or a pharmaceutically acceptable salt thereof could be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, it could be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains
5 from 0.001 to 50 mg, more preferably 0.005 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral
10 dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.005 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with one or more other therapeutically active agents, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic agent, an anti-inflammatory agent (including a steroid), an anticholinergic agent or an antiinfective agent (e.g. antibiotics or antivirals).
15

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof with one or more other therapeutically active agents, for example, a β_2 -adrenoreceptor agonist, an anti-histamine, an anti-allergic agent, an anti-inflammatory agent (including a steroid), an anticholinergic agent or an antiinfective agent (e.g. antibiotics or antivirals).
20

25 Examples of β_2 -adrenoreceptor agonists include salmeterol (e.g. as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2 -
30 adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Examples of anti-histamines include methapyrilene, loratadine, cetirizine, desloratadine or fexofenadine.
35

Examples of anti-inflammatory steroids include fluticasone propionate and budesonide.

Examples of anticholinergic compounds which may be used in combination with a compound of formula (I) or a pharmaceutically acceptable salt thereof are described in
40 WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312

A1. For example, anticholinergic agents include muscarinic M3 antagonists, such as ipratropium bromide, oxitropium bromide or tiotropium bromide.

- 5 Other suitable combinations include, for example, combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with other anti-inflammatory agents (e.g. anti-inflammatory corticosteroids, NSAIDs, leukotriene antagonists (e.g. montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists, chemokine antagonists such as CCR3 antagonists, adenosine 2a agonists, 5-lipoxygenase inhibitors and antiinfective agents such as an antibiotic or an
- 10 antiviral). An iNOS inhibitor is preferably for oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.
- 15 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.
- 20 The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions.

Biological Test Methods

PDE3, PDE4B, PDE4D, PDE5 Primary assay methods

5

The activity of the compounds can be measured as described below. Preferred compounds of the invention are selective PDE4 inhibitors, *i.e.* they inhibit PDE4 (*e.g.* PDE4B and/or PDE4D) more strongly than they inhibit other PDE's such as PDE3 and/or PDE5.

10

PDE enzyme sources and literature references

15

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also in M.M. McLaughlin et al., "A low K_m , rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. For example, in Example 1 of WO 94/20079, human recombinant PDE4B is described as being expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62, *e.g.* after induction by addition of 150 μ M CuSO_4 , and 100,000 $\times g$ supernatant fractions of yeast cell lysates are described for use in the harvesting of PDE4B enzyme.

20

25

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phosphodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

30

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

35

PDE3 may be purified from bovine aorta as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

40

PDE6 may be purified from bovine retina as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

Inhibition of PDE3, PDE4B, PDE 4D, PDE5 or PDE 6 activity: radioactive Scintillation Proximity Assay (SPA)

5 The ability of compounds to inhibit catalytic activity at PDE4B or 4D (human recombinant), PDE3 (from bovine aorta) PDE5 (human recombinant) or PDE 6 (from bovine retina) may be determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds (preferably as a solution in DMSO, e.g. 2 microlitre (μ l) volume) were preincubated at ambient temperature in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM

10 Tris-HCl buffer pH 7.5, 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes. The enzyme concentration was adjusted so that control rates are linear over the assay incubation period. For the PDE3, PDE4B and PDE4D assays [5',8- 3H]adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK559 or Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8

15 4SP, UK) was added to give 0.05 μ Ci per well and \sim 10nM final concentration. For the PDE5 and PDE6 assays [8- 3H]guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK392) was added to give 0.05 μ Ci per well and \sim 36nM final concentration. Plates e.g. containing approx. 100 μ l volume of assay mixture were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour.

20 Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ0150) were added (\sim 1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for 35 minutes to 1 hour to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 MicroBeta scintillation counter. For inhibition curves, 10 concentrations (e.g. 1.5nM -

25 30 μ M) of each compound were assayed; more potent compounds were assayed over lower concentration ranges (assay concentrations were generally between 30 μ M and 50fM). Curves were analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom). Results were expressed as pIC_{50} values.

30 Alternatively, the activity of the compounds can be measured in the following Fluorescence Polarisation (FP) assay:

Inhibition of PDE4B or PDE4D activity: Fluorescence Polarisation (FP) assay

35 The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant) and PDE4D (human recombinant) was determined by IMAP Fluorescence Polarisation (FP) assay (Molecular Devices Ltd code: R8062) in 384-well format. Test compounds (small volume, e.g. 0.5 μ l, of solution in DMSO) were preincubated at ambient temperature in

40 black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in

10mM Tris-HCl buffer pH 7.2, 10mM MgCl₂, 0.1% (w/v) bovine serum albumin, 0.05% NaN₃ for 10-30 minutes. The enzyme level was set so that reaction was linear throughout the incubation.

- 5 Fluorescein adenosine 3',5'-cyclic phosphate (Molecular Devices Ltd code: R7091) was added to give ~ 40nM final concentration. Plates were mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (Molecular Devices Ltd code: R7207) was added (60µl of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates were allowed to stand at ambient temperature for 1hour. The FP ratio of parallel to perpendicular light was measured using an AnalystTM plate reader (from Molecular Devices Ltd). For inhibition curves, 11 concentrations (0.5nM - 30µM) of each compound were assayed; more potent compounds were assayed over lower concentration ranges (assay concentrations were generally between 30µM and 50fM). Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited). Results were expressed as pIC₅₀ values.

For a given PDE4 inhibitor, the PDE4B (or PDE4D) inhibition values measured using the SPA and FP assays can differ slightly. However, in a regression analysis of at least 100 test compounds, the pIC₅₀ inhibition values measured using SPA and FP assays have been found generally to agree within 0.5 log units, for PDE4B and PDE4D (linear regression coefficient 0.966 for PDE4B and 0.971 for PDE4D; David R.Mobbs et al., "Comparison of the IMAP Fluorescence Polarisation Assay with the Scintillation Proximity Assay for Phosphodiesterase Activity", poster presented at the 2003 Molecular Devices UK & Europe User Meeting, 2nd October 2003, Down Hall, Harlow, Essex, United Kingdom).

Examples of compounds of the invention described above inhibit the catalytic activity at the PDE4B (human recombinant) enzyme with pIC₅₀'s in the range 7.5-10.8. Biological Data obtained for some of the Examples (PDE4B and PDE5 inhibitory activity) is as follows:

| Example No. | PDE4B mean pIC ₅₀ | PDE5 mean pIC ₅₀ |
|-------------|------------------------------|-----------------------------|
| 2 | 9.0 | 4.8 |
| 4 | 8.6 | 4.9 |
| 9 | 8.2 | 4.6 |

Emesis: Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5, 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential that a PDE4 inhibitory compound of the invention causes only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud *et al.*, "Emesis induced by inhibitors of PDE IV in the ferret" *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "examples"

Abbreviations used herein:

| | |
|-------|---|
| HPLC | high performance liquid chromatography |
| NMR | nuclear magnetic resonance |
| LC/MS | liquid chromatography/mass spectroscopy |
| TLC | thin layer chromatography |
| SPE | solid phase extraction column. Unless otherwise specified the solid phase will be silica gel. Aminopropyl SPE refers to a silica SPE column with aminopropyl residues immobilised on the solid phase (eg. IST Isolute™ columns). It is thought that compounds isolated by SPE are free bases. |
| SCX | solid phase extraction (SPE) column with benzene sulfonic acid residues immobilised on the solid phase (eg. IST Isolute™ columns). When eluting with ammonia/ methanol, it is thought that compounds isolated by SCX are free bases. |

General experimental details

LC/MS (liquid chromatography/mass spectroscopy)

Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.

- 5 UV wavelength : 215-330nm
Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5µl
Solvent A : 95% acetonitrile + 0.05% formic acid
- 10 Solvent B : 0.1% formic acid + 10mM ammonium acetate
Gradient: Mixtures of Solvent A and Solvent B are used according to the following gradient profiles (expressed as % Solvent A in the mixture): 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min; 100-0% A/0.2min
- 15 Mass Directed Automated Preparative HPLC column, conditions and eluent
Method A
The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5µm)
UV detection wavelength : 200-320nm
- 20 Flow rate : 20ml/min
Injection Volume: 0.5ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 0.05% formic acid
Gradient systems: mixtures of Solvent A and Solvent B are used according to a choice of
- 25 5 generic gradient profiles (expressed as % Solvent B in the mixture), ranging from a start of 0 to 50% Solvent B, with all finishing at 100% Solvent B to ensure total elution.
It is thought that compounds isolated by this method are free bases, unless the R¹ or R³ groups contain basic moieties, in which case formate salts may be formed.
- 30 Mass Directed Automated Preparative HPLC column, conditions and eluent
Method B
The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5µm)
UV detection wavelength : 200-320nm
- 35 Flow rate : 20ml/min
Injection Volume: 0.5ml
Solvent A : water + 0.1% trifluoroacetic acid
Solvent B : acetonitrile + 0.1% trifluoroacetic acid
Gradient systems: mixtures of Solvent A and Solvent B are used according to a choice of
- 40 5 generic gradient profiles (expressed as % Solvent B in the mixture), ranging from a start of 0 to 50% Solvent B, with all finishing at 100% Solvent B to ensure total elution.

It is thought that compounds isolated by this method are trifluoroacetate salts.

Product isolation by filtration directly from the reaction mixture

5 It is thought that compounds isolated by this method from reactions involving displacement of a 4-chloroquinoline intermediate with an amine of formula R^1R^2NH are hydrochloride salts.

'Hydrophobic Frit'

10 This refers to a Whatman PTFE filter medium (frit), pore size $5.0\mu m$, housed in a polypropylene tube.

Evaporation of product fractions after purification

15 Reference to column chromatography, SPE and preparative HPLC purification includes evaporation of the product containing fractions to dryness by an appropriate method.

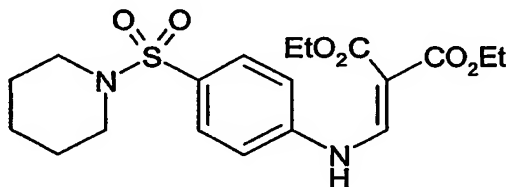
Aqueous ammonia solutions

20 '880 Ammonia' or '0.880 ammonia' refers to concentrated aqueous ammonia (specific gravity 0.880).

Intermediates and Examples

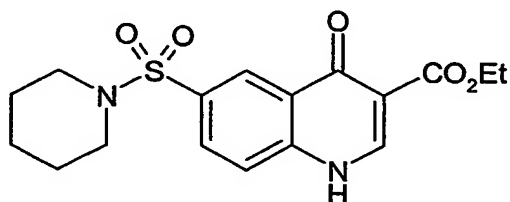
25 All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

Intermediate 1. Diethyl ({[4-(1-piperidinylsulfonyl)phenyl]amino}methylidene)propanedioate



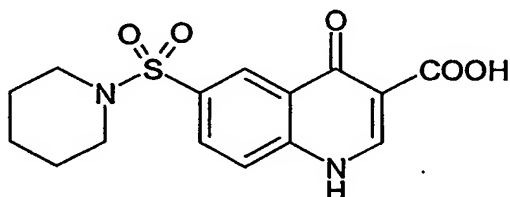
30 4-(1-Piperidinylsulfonyl)aniline (0.20g) (available from Maybridge International) and diethyl (ethoxymethylene)malonate (0.18g) (available from Aldrich) were heated at $150^{\circ}C$ under 150W microwave irradiation for 15mins. The mixture was diluted with cyclohexane, filtered and the residue dried at $40^{\circ}C$ *in vacuo* to give the title compound as a pale pink solid (0.284g).

35 LC/MS Rt 3.36min m/z 411 $[MH^+]$

Intermediate 2. Ethyl 4-oxo-6-(1-piperidinylsulfonyl)-1,4-dihydro-3-quinolinecarboxylate

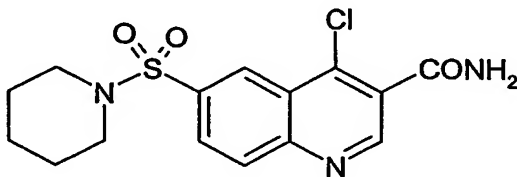
- 5 **Intermediate 1** (0.284g) was suspended in diphenyl ether (15ml) and heated at 250°C for 2h. After cooling, the mixture was diluted with cyclohexane (50ml) and the resulting precipitate filtered off and dried *in vacuo* to give the title compound as a brown solid (0.138g).
LC/MS Rt 2.68min *m/z* 365 [MH⁺]

10 **Intermediate 3. 4-Oxo-6-(1-piperidinylsulfonyl)-1,4-dihydro-3-quinolinecarboxylic acid**



- 15 **Intermediate 2** (0.138g) was dissolved in ethanol (2ml) and 2M sodium hydroxide (2ml) and the mixture heated under reflux for 3h. After cooling the solvent was removed under a stream of nitrogen and the residue dissolved in water (2ml) and extracted with ethyl acetate (2 x 4ml). The aqueous layer was acidified to pH 6.0 using 2M hydrochloric acid, and the resulting precipitate removed by filtration and dried *in vacuo* at 40°C to give the title compound (0.052g).
LC/MS Rt 2.83min *m/z* 337 [MH⁺]

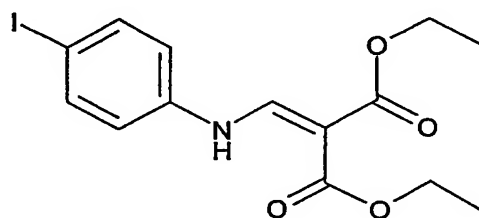
20 **Intermediate 4. 4-Chloro-6-(1-piperidinylsulfonyl)-3-quinolinecarboxamide**



- 25 **Intermediate 3** (0.051g) was suspended in thionyl chloride (4ml) and treated with *N,N*-dimethylformamide (4 drops), and the mixture heated at 80°C for 18h. The solvent was removed *in vacuo* and the residue azeotroped with toluene (5ml). The resulting solid was

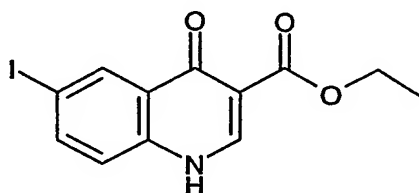
added to 880 ammonia (4ml) and the mixture stirred at room temperature for 3h. The solid was removed by filtration to give the title compound as a brown solid (0.011g).
LC/MS Rt 2.63min m/z 354 [MH^+]

5 **Intermediate 5. Diethyl {[4-iodophenyl]amino}methylenepropanedioate**



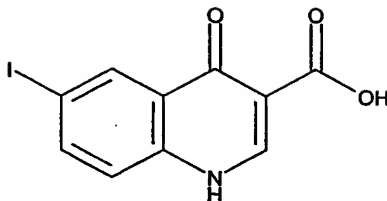
10 A mixture of 4-iodoaniline (208g) (available from Aldrich) and diethyl (ethoxymethylene)malonate (210ml) (available from Aldrich) was heated to 100°C. The mixture set solid at ca. 60°C, and was removed from heating and broken up. Heating was continued at 100°C for 1h, and the solid was collected, washed with cyclohexane (1000ml) and ethanol (2x500ml), and dried *in vacuo* at 40°C overnight to give the title compound as a white solid (356g).
15 LC/MS Rt 3.57min m/z 390 [MH^+].

Intermediate 6. Ethyl 6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylate



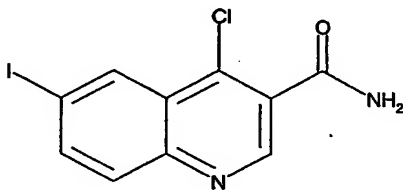
20 Diphenyl ether (170ml) was heated to reflux and intermediate 5 (30g) was gradually added down an air condenser. Once all the reagent had been added the mixture was heated under reflux for a further 30min. The mixture was then cooled and isohexane (200ml) was added. The solid formed was collected by filtration to give the title compound (19.2g).
25 NMR: (d-6 DMSO) δ 8.58 (1H,s), 8.42(1H,d), 7.99 (1H,dd), 7.44(1H,d), 4.21(2H,q), 1.28 (3H,t).

Intermediate 7. 6-Iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid



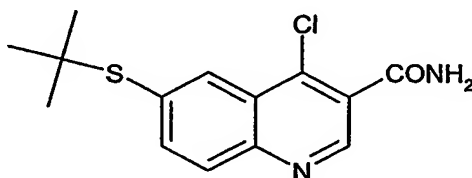
Sodium hydroxide (9.8g) was dissolved in water (61ml) and ethanol (30ml) was added. The resultant solution was added to intermediate 6 (10.0g), and the mixture was heated under reflux for 60min with stirring under nitrogen. Concentrated hydrochloric acid was added, giving a white precipitate. After stirring for 16h, the precipitate was filtered off, washed with water and dried *in vacuo* to give the title compound as a white solid (8.15g). LC/MS Rt 3.01min *m/z* 316 [MH⁺].

10 **Intermediate 8. 4-Chloro-6-iodo-3-quinolinecarboxamide**



Intermediate 7 (8.1g) was added portionwise to stirred thionyl chloride (60ml). *N,N*-dimethylformamide (3 drops) was added and the mixture was heated under reflux with stirring under nitrogen for 1.75h. The excess thionyl chloride was evaporated *in vacuo* and the residue was azeotroped with toluene (2x50ml). The resulting pale yellow solid was added portionwise to stirred 880 ammonia (250ml), and the mixture stirred at room temperature for 1.5h. The solid was filtered off, washed with water and dried *in vacuo* at 60°C for 16h to give the title compound as a white solid (7.94g). LC/MS Rt 2.72min *m/z* 332 [MH⁺].

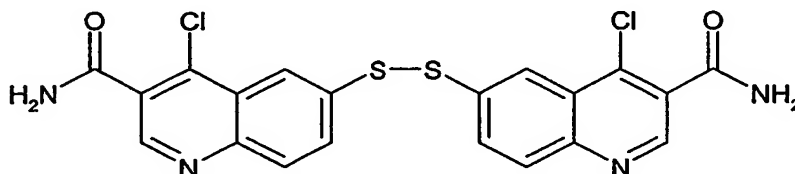
Intermediate 9. 4-Chloro-6-[(1,1-dimethylethyl)thio]-3-quinoline carboxamide



To a stirred mixture of intermediate 8 (14.7g) and tetrakis(triphenylphosphine) palladium (0) (1.02g) in toluene (250ml) under nitrogen was added a solution of (*tert*-butylsulphonyl)tributyltin (*JACS* 2002, **124**, 4874) (20.1g) in toluene (50ml), and the mixture was heated under reflux for 1 h. The mixture was cooled to room temperature, partitioned between 5% potassium fluoride solution (1000ml) and diethyl ether (500ml) and the organic solvent evaporated *in vacuo*. The solid obtained was triturated with diethyl ether and filtered to give the title compound as a pale orange solid (9.47g). The filtrate was evaporated *in vacuo*. Purification by chromatography on silica gel, eluting with diethyl ether then ethyl acetate, gave further title compound as an orange solid (2.97g; total yield 12.4g).

LC/MS Rt 3.04min *m/z* 295 [MH^+]

Intermediate 10. 6,6'-Dithiobis(4-chloro-3-quinolinecarboxamide)

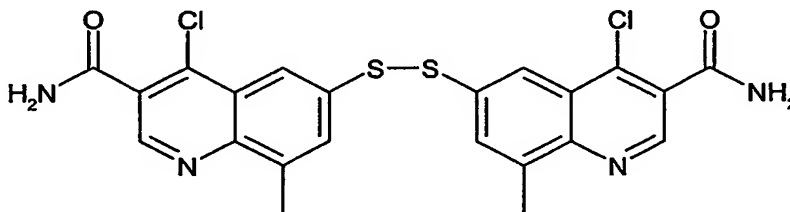


Intermediate 9 (12.3g) was dissolved in trifluoroacetic acid (200ml), phenyl sulfoxide (21.2g) added, and the mixture cooled to 0°C. Methyltrichlorosilane (49ml) was added over 10mins, and the mixture stirred for 1h. The mixture was evaporated *in vacuo*, the residue triturated with diethyl ether (250ml), and the solvent decanted off. The residue was triturated twice more with diethyl ether (200ml) and the solid filtered off to give the title compound as a pale yellow solid (10.5g).

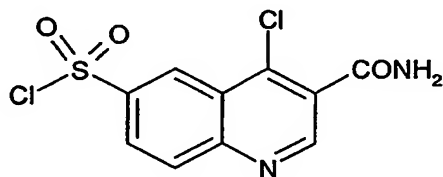
LC/MS Rt 2.87min *m/z* 475 [MH^+]

Similarly prepared using 4-iodo-2-methylaniline instead of 4-iodoaniline (as in the preparation of Intermediate 5) was:

Intermediate 10a. 6,6'-Dithiobis(4-chloro-8-methyl-3-quinolinecarboxamide)

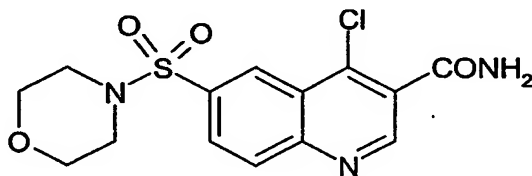


LC/MS Rt 3.50min *m/z* 503 [MH^+]

Intermediate 11. 3-(Aminocarbonyl)-4-chloro-6-quinolinesulfonyl chloride

5

Chlorine was bubbled through a suspension of intermediate 10 (0.20g) in acetic acid (4ml) and water (1ml) for 5min, giving a yellow solution. The mixture was partitioned between water (50ml) and diethyl ether (50ml) and the organic layer dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a pale yellow solid (0.248g).

10 LC/MS Rt 2.63min m/z 305 [MH^+]**Intermediate 12. 4-Chloro-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide**

15

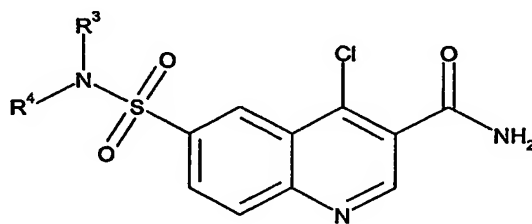
A solution of intermediate 11 (0.88g) in dichloromethane (10ml) and *N,N*-dimethylformamide (5ml) was added to a solution of morpholine (0.131ml) and *N,N*-diisopropylethylamine (1.31ml) in dichloromethane (30ml) at 0-5°C. The mixture was allowed to warm to 20°C over 18h, diluted with dichloromethane (150ml), and extracted with 1M hydrochloric acid (100ml) followed by saturated aqueous sodium bicarbonate solution (100ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a brown gum (0.571g).

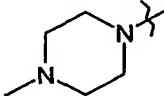
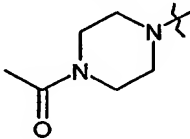
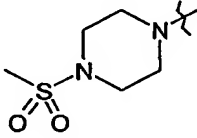

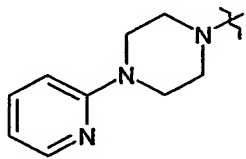
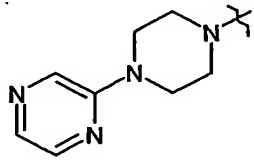
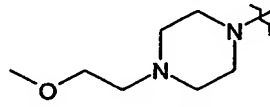
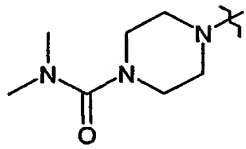
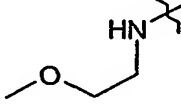
20

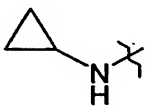
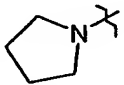
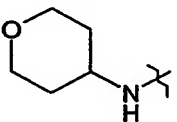
LC/MS Rt 2.22min m/z 356 [MH^+]

25

Similarly prepared from intermediate 11 were the following:

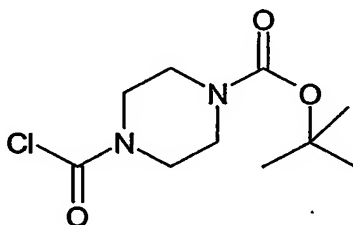


| Intermediate Number | R ³ R ⁴ N- | Amine Reagent R ³ R ⁴ NH/ Source (a) | LC/MS Rt min | LC/MS MH ⁺ |
|---------------------|---|--|--------------|-----------------------|
| 13 |  | 1-Methylpiperazine/ Aldrich | 1.76 | 369 |
| 14 |  | 1-Acetylpiperazine/ Aldrich | 2.26 | 397 |
| 15 |  | 1-(Methylsulphonyl) piperazine/ Patent: DE828695 (1950) | 2.38 | 433 |
| 16 |  | Dimethylamine.HCl/ Aldrich | 2.25 | 314 |
| 17 |  | (2-Pyridinyl) piperazine/Aldrich | 2.24 | 432 |
| 18 |  | 2-(1-Piperazinyl) pyrazine/Emkachem | 2.53 | 433 |
| 19 |  | 1-[2-(Methoxy) ethyl]piperazine/Em kachem | 1.90 | 413 |
| 20 |  | N,N-Dimethyl-1- piperazine- carboxamide/ <u>Intermediate 27</u> | 2.37 | 426 |
| 21 |  | [2-(methoxy)- ethyl]amine/Aldrich | 2.10 | 344 |

| | | | | |
|----|---|--|------|-----|
| 22 |  | Cyclopropylamine/ Aldrich | 2.26 | 326 |
| 23 |  | Cyclopentylamine/ Aldrich | 2.41 | 340 |
| 24 |  | Tetrahydro-2H- pyran-4-ylamine/ Combi- Block | 2.16 | 370 |

(a) Where available, a salt such as the hydrochloride salt of the amine R^3R^4NH may be used.

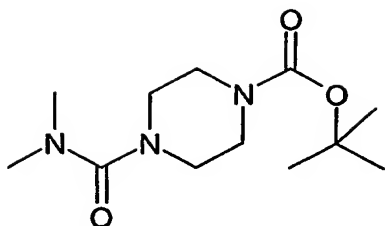
Intermediate 25. 1,1-Dimethylethyl 4-(chlorocarbonyl)-1-piperazinecarboxylate



A solution of 1,1-dimethylethyl 1-piperazinecarboxylate (13.0g) (available from Aldrich) and pyridine (11.2ml) in dichloromethane (30ml) was added dropwise to a solution of triphosgene (8.3g) in dichloromethane (60ml) at 0-5°C. The cooling bath was removed and the mixture warmed to room temperature over 30min. The mixture was quenched by the dropwise addition of 1M hydrochloric acid (50ml). The organic layer was separated and washed successively with 1M hydrochloric acid (40ml), water (40ml) and saturated sodium chloride solution (40ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a yellow solid (16.0g).

1H NMR ($CDCl_3$) δ 3.71 (2H,m, CH_2), 3.62 (2H,m, CH_2), 3.5 (4H,m,2x CH_2), 1.5 (9H,s,3x CH_3).

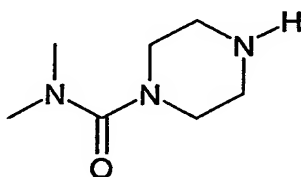
Intermediate 26. 1,1-Dimethylethyl 4-[(dimethylamino)carbonyl]-1-piperazinecarboxylate



To a solution of dimethylamine hydrochloride (0.15g) (available from Aldrich) in dichloromethane (5ml) was added triethylamine (0.305g) and the mixture stirred for 10min, after which intermediate 25 (0.3g) was added. The mixture was heated under reflux for 3hr, cooled, diluted with dichloromethane (20ml) and washed with water (20ml). The organic layer was dried and evaporated *in vacuo*; the residue was loaded in methanol onto a sulphonic acid ion exchange cartridge (Isolute SCX), and the cartridge was eluted with methanol. Evaporation of the solvent gave the title compound as a white solid (0.276g).

$^1\text{H NMR}$ (CDCl_3) δ 3.45 (4H, m, CH_2), 3.2 (4H, m, $2 \times \text{CH}_2$), 2.85 (6H, s, $2 \times \text{CH}_3$), 1.55 (9H, s, $3 \times \text{CH}_3$).

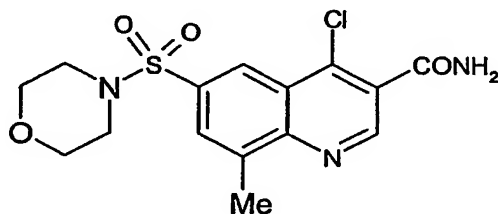
Intermediate 27. N,N-dimethyl-1-piperazinecarboxamide



To intermediate 26 (0.27g) was added 4M hydrogen chloride in 1,4 dioxane (10ml); after stirring for 3h the solvent was evaporated *in vacuo* to give the title compound as a white solid (0.238g).

$^1\text{H NMR}$ (MeOD) δ 3.5 (4H, m, CH_2), 3.3 (4H, m, $2 \times \text{CH}_2$), 2.95 (6H, s, $2 \times \text{CH}_3$), 3.35 (1H, m, NH)

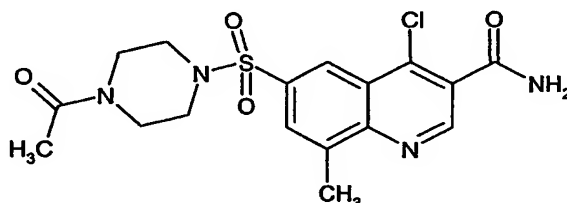
Intermediate 28. 4-Chloro-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide



Chlorine was bubbled through a suspension of intermediate 10a (3.0g) in acetic acid (40ml) and water (10ml) for 4min. The mixture was partitioned between water (300ml) and diethyl ether (300ml) and the organic layer dried (MgSO_4) and concentrated *in vacuo*. The residue was triturated with toluene (75ml) and the solvent removed *in vacuo* to give a yellow solid (2.7g). The yellow solid (1g) in dichloromethane (3ml) and *N,N*-dimethylformamide (0.5ml) was added to a solution of morpholine (0.272g) and *N,N*-diisopropylethylamine (1ml) in dichloromethane (15ml) at 0°C. The mixture was stirred at 0°C for 2h and then allowed to warm to room temperature over 3h. The mixture was partitioned between saturated aqueous sodium bicarbonate solution (40ml) and dichloromethane (40ml). The organic layer was collected, dried (MgSO_4) and the solvent removed *in vacuo*. Purification by chromatography on silica gel, eluting with 30% cyclohexane in ethyl acetate gave the impure title compound as a fawn foam (0.6g). LC/MS Rt 2.52 min m/z 370 [MH^+]; major by product LC/MS Rt 2.70 min m/z 455 [MH^+]

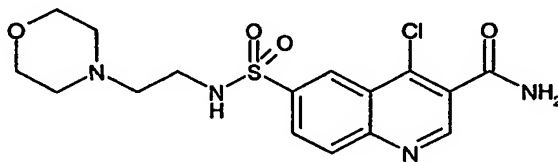
Similarly prepared from intermediate 10a and 1-acetypiperazine (Aldrich) was the following:

Intermediate 29. 6-[4-Acetyl-1-piperazinyl)sulfonyl]-4-chloro-8-methyl-3-quinolinecarboxamide



LC/MS Rt 2.41min m/z 411 [MH^+]

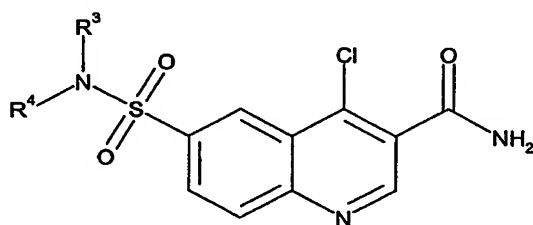
Intermediate 30. 4-Chloro-6-([2-(4-morpholinyl)ethyl]amino)sulfonyl]-3-quinolinecarboxamide



Chlorine was bubbled through a vigorously stirred suspension of intermediate 10 (2.5g) in acetic acid (40ml) and water (10ml) at room temperature for 10min. The mixture was partitioned between water (300ml) and diethyl ether (2x300ml) and the organic layers washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was triturated with toluene (2x150ml) and the solvent removed *in vacuo* to give the sulphonyl chloride

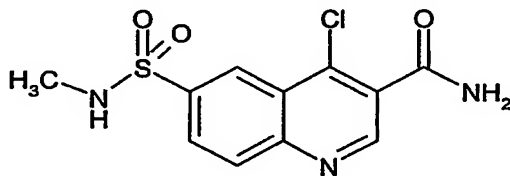
intermediate as a yellow solid (3.3g). The yellow solid was dissolved in a mixture of dichloromethane (100ml) and *N,N*-dimethylformamide (11ml), and an aliquot (11.1ml) of this solution was added to a solution of [2-(4-morpholinyl)ethyl]amine (Aldrich, 0.136g) and *N,N*-diisopropylethylamine (0.367ml) in dichloromethane (2ml) at 0°C. The mixture was stirred at 0°C for 2h and then allowed to warm to room temperature overnight. The mixture was partitioned between saturated aqueous sodium bicarbonate solution (20ml) and dichloromethane (10ml). The organic layer was separated using a hydrophobic frit, and the solvent removed *in vacuo* to give the title compound as a brown gum (0.334g). LC/MS Rt 1.77 min *m/z* 399 [MH⁺]

Similarly prepared from intermediate 10 were the following:



| Intermediate Number | R ³ R ⁴ N- | Amine Reagent R ³ R ⁴ NH/ Source | LC/MS Rt min | LC/MS MH ⁺ |
|---------------------|----------------------------------|--|--------------|-----------------------|
| 31 | | N,N-dimethyl-4-piperidinamine/ Lancaster | 1.89 | 397 |
| 32 | | [2-(1-pyrrolidinyl)ethyl]amine/ Aldrich | 1.79 | 383 |

Intermediate 33. 4-Chloro-6-[(methylamino)sulfonyl]-3-quinolinecarboxamide

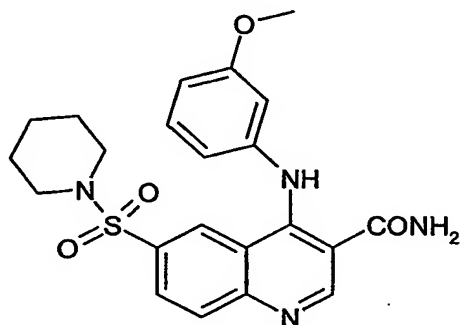


Chlorine was bubbled through a vigorously stirred suspension of intermediate 10 (0.1g) in acetic acid (4ml) and water (1ml) at room temperature for 2min. The mixture was partitioned between water (100ml) and diethyl ether (3x50ml) and the organic layers washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was triturated with toluene (2x15ml) and the solvent removed *in vacuo* to give the sulphonyl chloride intermediate as an orange gum (0.127g). The orange gum was dissolved in *N,N*-dimethylformamide (2.6ml), and an aliquot (1.3ml) of this solution was cooled to 0°C. Methylamine hydrochloride (Aldrich, 0.0074g) and *N,N*-diisopropylethylamine (0.058ml) were added, and the mixture was allowed to warm to room temperature with stirring overnight (18h). The mixture was applied directly to a solid phase extraction cartridge (Isolute, aminopropyl solid phase, 10g), and eluted sequentially with chloroform, ether, ethyl acetate, acetone and methanol. The acetone and methanol fractions were evaporated to give the title compound (0.0109g).

LC/MS Rt 2.04 min *m/z* 300 [MH⁺]

Examples

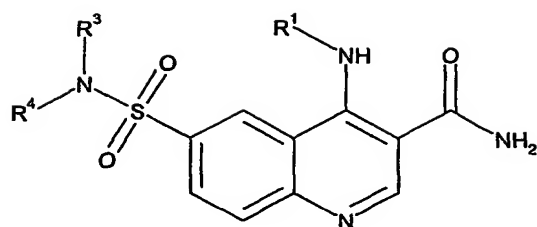
Example 1. 4-[[3-(Methyloxy)phenyl]amino]-6-(1-piperidinylsulfonyl)-3-quinolinecarboxamide hydrochloride



Intermediate 4 (0.011g) was suspended in acetonitrile (2ml), 3-methoxyaniline (0.004g) (available from Aldrich) was added and the mixture heated at 70°C for 5h. The mixture was cooled to room temperature, and the precipitate filtered off, washed with acetonitrile and dried to give the title compound (0.008g).


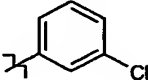

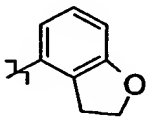
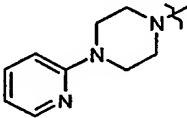
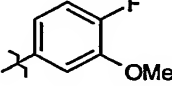
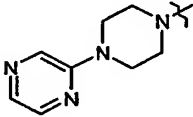
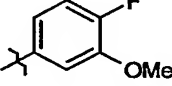
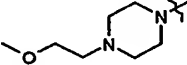
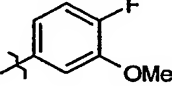
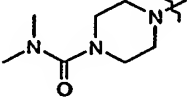
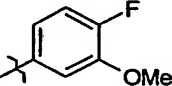
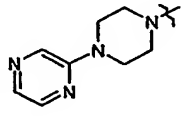
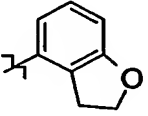
LC/MS Rt 2.75min *m/z* 441 [MH⁺]

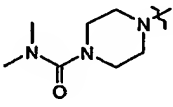
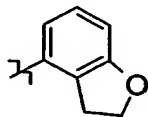
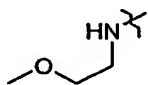
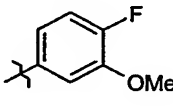
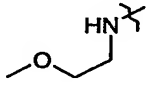
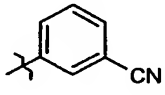
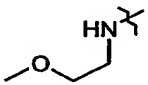
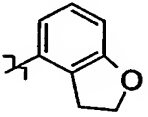
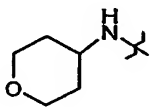
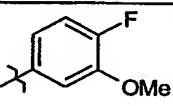
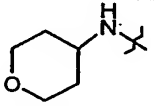
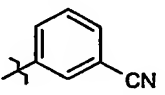
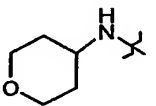
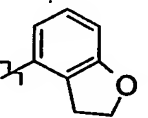
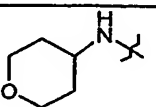
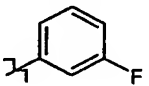
Similarly prepared from the intermediate numbers shown in the table were the following:

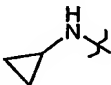
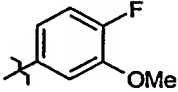
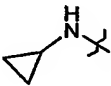
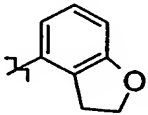
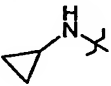
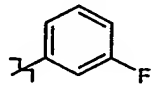
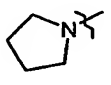
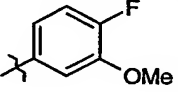
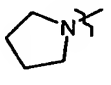
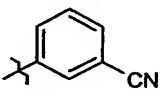
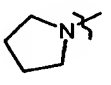
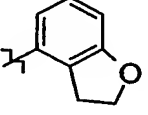
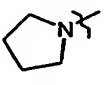
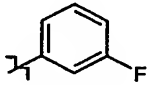
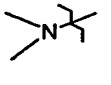
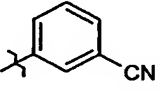
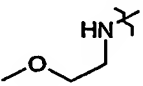
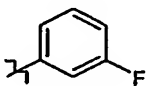


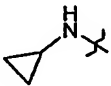
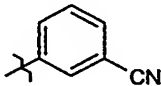

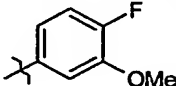
| Example Number (a) | Intermediate number | R ³ R ⁴ N- | R ¹ | Amine Reagent R ¹ NH ₂ / Source | Isolation Method (b) | LC/MS MH ⁺ | LC/MS Rt min |
|--------------------|---------------------|----------------------------------|----------------|---|----------------------|-----------------------|--------------|
| 2 (HCl) | 16 | | | 3-(methoxy)aniline/ Aldrich | (I) | 401 | 2.41 |
| 3 | 12 | | | 3-(methoxy)aniline/ Aldrich | (II) | 443 | 2.44 |
| 4 (HCl) | 12 | | | 3-chloroaniline/ Aldrich | (II) * | 447 | 2.64 |
| 5 (HCl) | 12 | | | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (II) * | 455 | 2.41 |
| 6 (HCl) | 12 | | | 3-fluoroaniline/ Aldrich | (II) * | 431 | 2.51 |
| 7 (HCl) | 12 | | | 1-methyl-1H-indazol-6-amine hydrochloride/ <i>Synthetic Communications</i> (1996), 26(13), 2443-2447. | (I) | 467 | 2.29 |

| | | | | | | |
|-------------|----|--|--|-------|-----|------|
| 8 (HCl) | 12 | | 1-methyl-1H-benzimidazol-6-amine/ <i>Heterocycles</i> (1991), 32(5), 1003-12. | (I) | 467 | 1.90 |
| 9 (HCl) | 16 | | 3-fluoroaniline/ Aldrich | (I) | 443 | 2.39 |
| 10 (HCl) | 13 | | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (II)* | 473 | 2.03 |
| 11 (HCl) | 14 | | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 501 | 2.32 |
| 12 (HCl) | 15 | | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 537 | 2.53 |
| 13 (HCl) | 14 | | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (I) | 495 | 2.30 |
| 14 (HCl) | 15 | | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (I) | 531 | 2.51 |
| 15 (HCl) | 12 | | 4-fluoro-3-methoxyaniline/ APOLLO-CHEM | (I) | 461 | 2.35 |

| | | | | | | | |
|-------------|----|---|---|---|-------|-----|------|
| 16 (HCl) | 16 |  |  | 3-chloroaniline/ Aldrich | (I) | 405 | 2.64 |
| 17 (HCl) | 16 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (I) | 412 | 2.37 |
| 18 (HCl) | 17 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 537 | 2.56 |
| 19 (HCl) | 18 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (II)* | 538 | 2.66 |
| 20 (HCl) | 19 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 518 | 2.11 |
| 21 (HCl) | 20 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 531 | 2.50 |
| 22 (HCl) | 18 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (II)* | 532 | 2.64 |

| | | | | | | | |
|-------------|----|---|---|---|-------|-----|------|
| 23 (HCl) | 20 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (I) | 525 | 2.48 |
| 24 (TFA) | 21 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (III) | 449 | 2.22 |
| 25 (TFA) | 21 |  |  | 3-aminobenzonitrile/ Aldrich | (III) | 426 | 2.23 |
| 26 (TFA) | 21 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5. | (III) | 443 | 2.20 |
| 27 (HCl) | 24 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 475 | 2.26 |
| 28 (TFA) | 24 |  |  | 3-aminobenzonitrile/ Aldrich | (III) | 452 | 2.27 |
| 29 (TFA) | 24 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5 | (III) | 469 | 2.24 |
| 30 (HCl) | 24 |  |  | 3-fluoroaniline/ Aldrich | (I) | 445 | 2.31 |

| | | | | | | | |
|-------------|----|---|---|--|-------|-----|------|
| 31 (TFA) | 22 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (III) | 431 | 2.35 |
| 32 (TFA) | 22 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5 | (III) | 425 | 2.32 |
| 33 (TFA) | 22 |  |  | 3-fluoroaniline/ Aldrich | (III) | 401 | 2.43 |
| 34 (HCl) | 23 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (I) | 445 | 2.51 |
| 35 (HCl) | 23 |  |  | 3-aminobenzonitrile/ Aldrich | (I) | 422 | 2.57 |
| 36 (HCl) | 23 |  |  | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5 | (I) | 439 | 2.49 |
| 37 (HCl) | 23 |  |  | 3-fluoroaniline/ Aldrich | (I) | 415 | 2.62 |
| 38 (HCl) | 16 |  |  | 3-aminobenzonitrile/ Aldrich | (I) | 396 | 2.42 |
| 39 (TFA) | 21 |  |  | 3-fluoroaniline/ Aldrich | (III) | 419 | 2.26 |

| | | | | | | | |
|-------------|----|---|---|---|-------|-----|------|
| 40 (TFA) | 22 |  |  | 3-aminobenzonitrile/ Aldrich | (III) | 408 | 2.39 |
| 41 (TFA) | 16 |  |  | 4-fluoro-3-methoxyaniline/ Apollo-Chem | (III) | 419 | 2.37 |

(a) Salt forms: HCl = hydrochloride

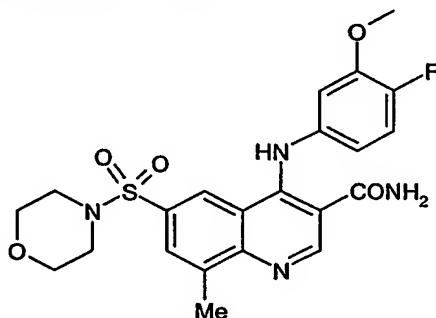
TFA = trifluoroacetate

5 (b) Isolation Method: (I) Filtered off directly from the reaction mixture; it is thought that compounds isolated by this method are hydrochloride salts.

(II) Mass Directed HPLC Method A; it is thought that compounds isolated by this method are free bases unless the R¹ or R³ groups contain basic moieties, in which case formate salts may be formed. *2M aqueous hydrochloric acid was added to
10 the product fractions to form the HCl salt where indicated.

(III) Mass Directed HPLC Method B; it is thought that compounds isolated by this method are trifluoroacetate salts.

15 **Example 42.** 4-([4-Fluoro-3-(methoxy)phenyl]amino)-8-methyl-6-(4-morpholinylsulfonyl)-3-quinolinecarboxamide

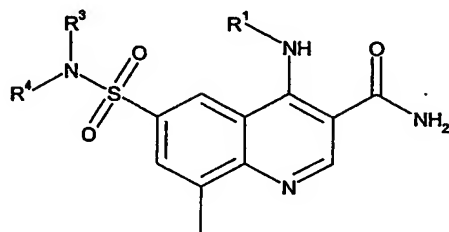


Intermediate 28 (0.050g) was suspended in acetonitrile (2ml),

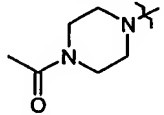
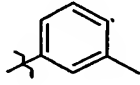
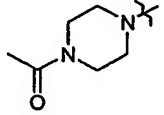
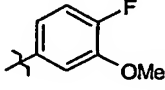
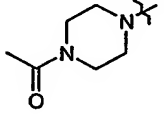
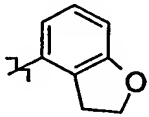
20 4-fluoro-3-(methoxy)aniline (0.025g) (available from Aldrich) was added and the mixture heated at 80°C for 16h. The mixture was cooled to room temperature and the solvent blown off under a stream of nitrogen. Purification by mass directed HPLC gave a yellow oil. This was loaded onto an SPE cartridge (1g Varian Bond Elut, aminopropyl solid phase) and eluted with methanol to give the title compound as a yellow solid (0.018g).
LC/MS Rt 2.58min *m/z* 475 [MH⁺]

25

Similarly prepared from the intermediate numbers shown in the table were the following:



| Example Number (a) | Intermediate number | R ³ R ⁴ N- | R ¹ | Amine Reagent R ¹ NH ₂ / Source | Isolation Method (b) | LC/MS Rt min | LC/MS MH ⁺ |
|-----------------------|---------------------|----------------------------------|----------------|--|-------------------------|-----------------|--------------------------|
| 43 | 28 | | | 2,3-dihydro-1-benzofuran-4-amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5 | (1) | 2.57 | 469 |
| 44 | 28 | | | 3-methylaniline/ Aldrich | (1) | 2.56 | 441 |
| 45 | 28 | | | 3-fluoroaniline/ Aldrich | (1) | 2.68 | 445 |
| 46 | 28 | | | 3-cyanoaniline/ Aldrich | (1) | 452 | 2.62 |
| 50 HCl | 28 | | | 3-chloroaniline/ Aldrich | (II) | 461 | 2.83 |
| 51 HCl | 28 | | | 1-methyl-1H-indazol-6-amine hydrochloride/ <i>Synthetic Communications</i> (1996), 26(13), 2443-2447. | (II) | 481 | 2.49 |

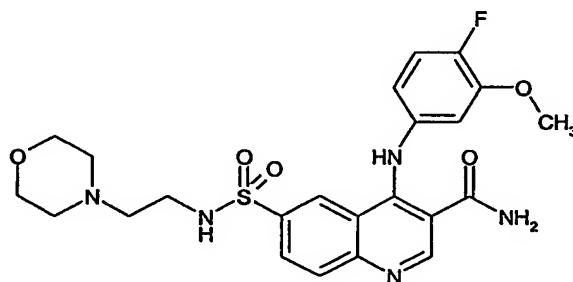
| | | | | | | | |
|----|----|---|---|--|-----|-----|------|
| 52 | 29 |  |  | 3-methylaniline/ Aldrich | (I) | 482 | 2.44 |
| 53 | 29 |  |  | 4-fluoro-3- methoxyaniline/ Apollo-Chem | (I) | 516 | 2.44 |
| 54 | 29 |  |  | 2,3-dihydro-1- benzofuran-4- amine hydrobromide/ <i>Journal of Heterocyclic Chemistry</i> (1980), 17(6), 1333-5 | (I) | 510 | 2.44 |

(a) Salt form: HCl = hydrochloride

(b) Isolation Method (1): Mass Directed HPLC Method A, followed by aminopropyl SPE to give the product as the free base.

- 5 (II) Mass Directed HPLC Method A; hydrochloric acid was added to the product fractions to generate the hydrochloride salt

10 **Example 47.** 4-[[4-Fluoro-3-(methoxy)phenyl]amino]-6-([2-(4-morpholinyl)ethyl]amino)sulfonyl]-3-quinolinecarboxamide hydrochloride

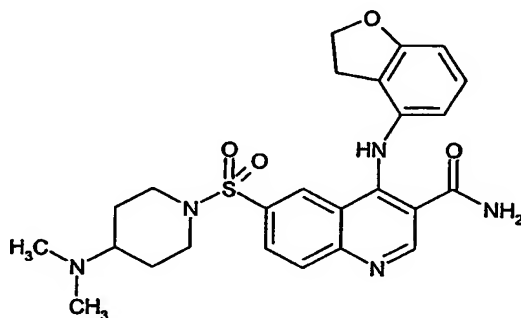


- 15 4-Fluoro-3-methoxyaniline (Apollo-Chem, 0.0085g) was added to intermediate 30 (0.021g) in ethanol (3ml), pyridine hydrochloride 0.012g) was added, and the mixture was heated under reflux for 5h. The solvent was evaporated to give a brown gum (0.033g), which was purified by mass directed preparative HPLC (Method A); 2N hydrochloric acid

(1ml) was added to the product fractions, and the solvents evaporated to give the title compound (0.0067g).

LC/MS Rt 1.91min m/z 504 $[MH^+]$

5 **Example 48.** 4-(2,3-Dihydro-1-benzofuran-4-ylamino)-6-([4-(dimethylamino)-1-piperidinyl]sulfonyl)-3-quinolinecarboxamide hydrochloride



10

To intermediate 31 (0.042g) in ethanol (3ml) was added 2,3-dihydro-1-benzofuran-4-amine (Journal of Heterocyclic Chemistry (1980), 17(6), 1333-5, 0.016g) and concentrated hydrochloric acid (0.1ml), and the mixture was heated under reflux for 3h. The solvent was evaporated to give the crude product (0.070g), which was purified by mass directed HPLC (Method A); 2N hydrochloric acid (0.5ml) was added to the product fractions, and the solvents evaporated to give the title compound (0.0041g).

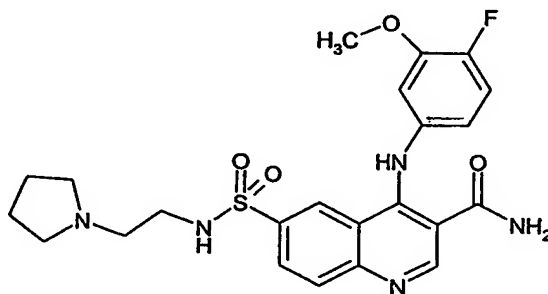
15

LC/MS Rt 1.89min m/z 496 $[MH^+]$

Similarly prepared from intermediate 32 and 4-fluoro-3-methoxyaniline (Apollo-Chem) (except that no hydrochloric acid was added to the preparative HPLC fractions) was:

20

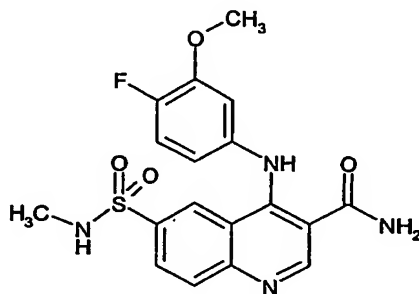
Example 49. 4-([4-Fluoro-3-(methoxy)phenyl]amino)-6-([2-(1-pyrrolidinyl)ethyl]amino)sulfonyl)-3-quinolinecarboxamide formate



25

LC/MS Rt 1.79min m/z 488 $[MH^+]$

Example 55. 4-{[4-Fluoro-3-(methyloxy)phenyl]amino}-6-[(methylamino)sulfonyl]-3-quinolinecarboxamide hydrochloride



5

To a solution of intermediate 33 (0.011g) in acetonitrile (2ml) and *N,N*-dimethylformamide (1.5ml) was added 4-fluoro-3-methoxyaniline (Apollo-Chem, 0.007g), and the mixture was heated at 80° with stirring under nitrogen for 18h. The solvents were evaporated to give a brown gum, which was purified by mass directed preparative HPLC (Method A); 2N

10

hydrochloric acid (0.5ml) was added to the product fractions, and the solvents evaporated to give the title compound as a pale yellow solid (0.0058g).
LC/MS Rt 2.17min *m/z* 405 [MH⁺]